REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the remaining rejections and allow Claims 16-24, the only claims pending and under examination in this application.

AMENDMENTS

The claims have been amended to give one-letter designations to the target protein (i.e., T), binding protein (i.e., P) and blocking protein (i.e., B) in order to clarify the claim language. Furthermore, Claim 16 has been amended to positively recite that the blocking protein ligand and target protein ligand of the bifunctional molecule are covalently bonded to each other, to make the bifunctional inhibitor (I). In addition, the claim has been amended to clarify that the bifunctional molecule non-covalently binds to the both the target protein and blocking protein, to form a tripartite complex. Support for this feature is found at page 7, line 11 and Figure 1, among other locations in the specification. Finally, Claim 16 has been amended to specify that the binding of the target protein (T) to the binding protein (P) is inhibited by the tripartite complex, which prevents access of the binding protein (P) to the target protein (T). Support for this amendment is found in the specification at page 17, lines 24-30 and Figure 1.

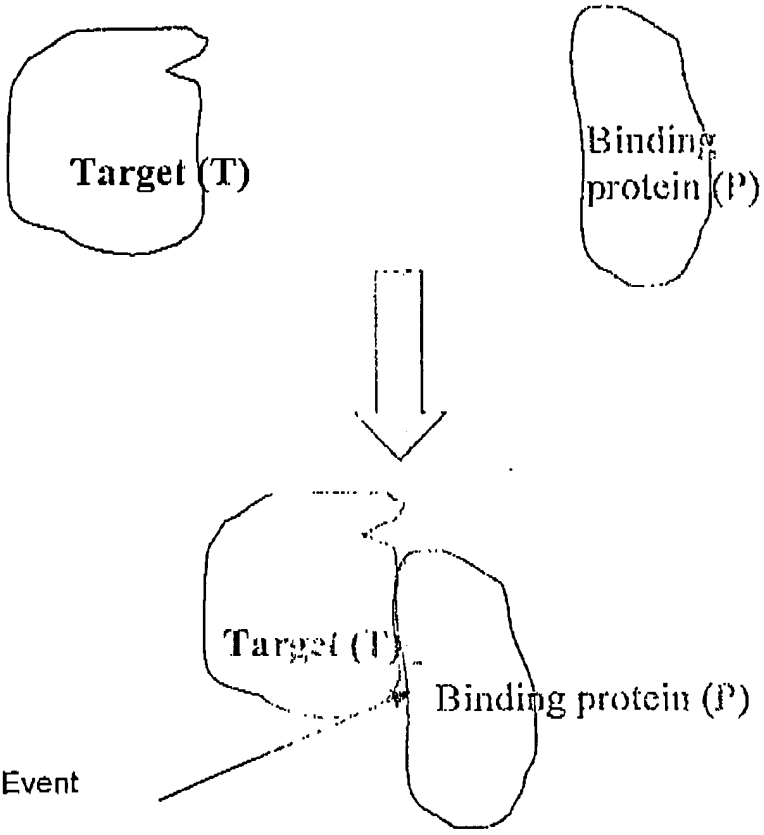
As the above amendments introduce no new matter to the application, their entry by the Examiner is respectfully requested.

REVIEW OF INVENTION

The invention is directed to methods of inhibiting a protein-protein interaction in a host, e.g., for therapeutic purposes. For example, the invention is directed to methods of inhibiting an in vivo biochemical event caused by two proteins, e.g., a target protein (T) and a binding (or effector) protein (P). The

problem that is solved by the present invention is how to prevent the binding protein (P) from binding to the target protein (T). The solution to this problem is to administer a bifunctional inhibitor molecule (I), which non-covalently binds the target protein (T). Binding of I to Tprevents access to the target protein (T) by the binding protein (P). The bifunctional inhibitor molecule (I) has a target protein ligand with an affinity for target protein (T), and a blocking protein ligand with an affinity for a blocking protein (B).

The targeted binding event between a target protein (T) and a binding protein (P) that is the subject of the claims is illustrated below:



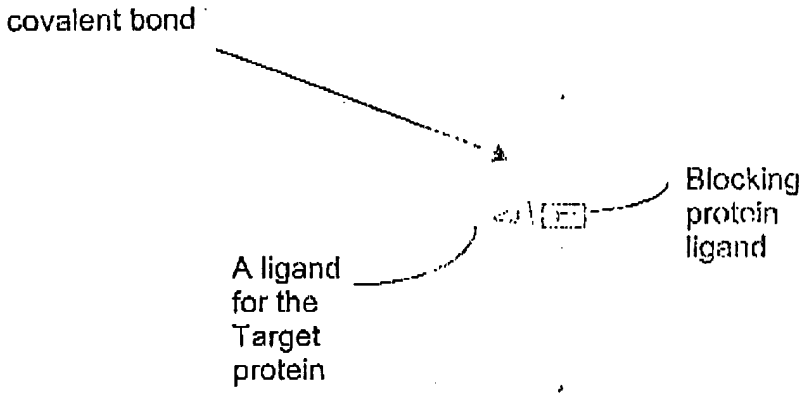
Targeted Binding Event

This binding event can also be represented as the interaction T+P --> TP.

Traditionally, disruption of this targeted binding event has been accomplished using inhibitor molecules, which in some way interfere with this

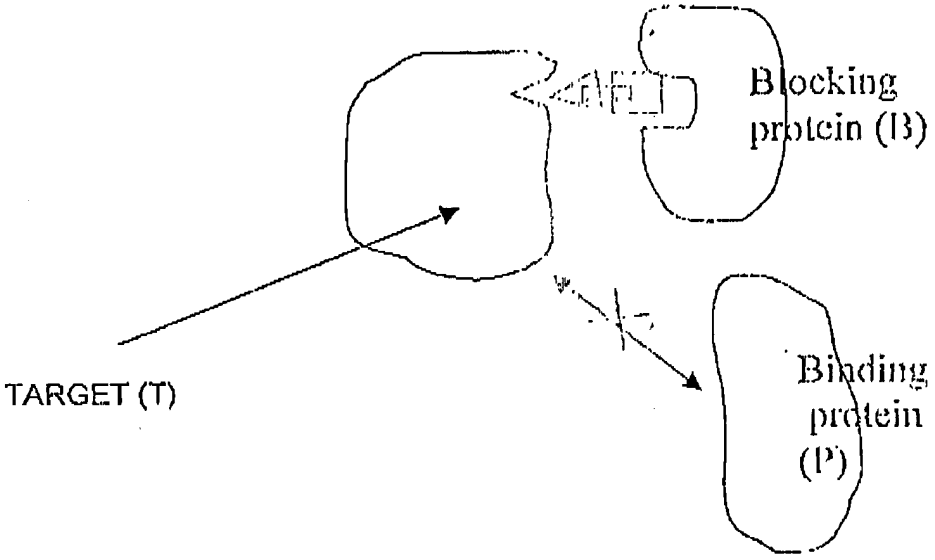
interaction, for example by binding T or P so that the TP complex does not form. However, the size of the inhibitor molecule needed to provide for the blocking activity can be limiting with respect to practical use in therapeutic applications. For example, large molecules may be used, and may be needed, to effectively inihibit the TP binding interaction, but large molecules may be difficult to administer in vivo, and may have bioavailability or other problems -- making their practical use difficult. As such, there has been an ongoing need in the field to identify small molecule inhibitors.

The present invention is based on the ingenious manner in which the inventors have satisfied this need for an effective small molecule inhibitor. The invention employs a bifunctional inhibitor molecule (I) that recruits a blocking protein (B) in vivo to produce an inhibiting complex. The bifunctional molecule is made up of a target protein ligand and a second ligand that binds to a blocking protein. A representation of the bifunctional molecules employed in the invention is provided below:



The inhibitor molecule (I) can also be represented as [T ligand]-[B-ligand]. This bifunctional molecule is a single *molecule*, as the two ligands are covalently bound to each other.

When administered to the host, the bifunctional molecule bonds non-covalently to the target protein and a blocking protein. This interaction inhibits binding of the binding protein to the target. This interaction is illustrated below:



This can also be represented as follows:

T--[T ligand]-[B ligand]--B

or

T--[I]--B

This is a complex between the inhibitor molecule (I) and the target and blocking proteins T,B. The bonds (---) are non-covalent.

The administered bifunctional molecule is a small molecule, i.e., less than 5000 daltons, which in vivo nonetheless turns into an effective inhibitor complex when it binds to the blocking protein, and sequesters the target protein. This bifunctional inhibitor molecule and its method of use therefore satisfy the felt-needs for improved inhibitors and methods of preventing binding interactions in the field of pharmaceutical active agents.

MAINTAINED REJECTIONS

The Examiner has maintained the rejection of Claims 16-24 under 35 U.S.C. § 112, 2nd ¶. The Examiner asserts that the claim is indefinite because "the method does not clearly outline how the second protein and the blocking protein interact such that inhibition of the first and second is accomplished."

It is respectfully submitted that, in view of the above amendment that specifies that the formation of the "T-I-B" complex prevents access of the binding protein P to target protein T, this rejection may be withdrawn.

As such, it is respectfully submitted that Claim 16 fully complies with the requirements of 35 U.S.C. §112, 2nd ¶, and that the rejection of Claim 16 for issue B may be withdrawn.

The rejection of Claims 16-21 and 24 under 35 U.S.C. §102 (b) as being anticipated by Varshavsky et al was also maintained.

This rejection is based on the equation by the Examiner of the Varshavsky's a-b-i trifunctional molecule to the claimed bifunctional molecules and methods. In the a-b-i molecules of the cited reference, the molecules include three distinct ligands: (I) for enzyme I, (a) for protein A and (b) for protein B.

Varshavsky discloses the a-b-i entity as a single "molecule" in which each of the three moieties, i.e., a, b and I, are bonded to each other by a solid line, indicating to or teaching one of skill in the art that each of a, b and I are bound to each other covalently. The result is a molecule that includes three distinct moieties, a, b and I covalently bonded to each other, which is a trifunctional molecule.

As such, Varshavsky fails to teach a method in which a bifunctional molecule is employed, as claimed.

Furthermore, the claimed methods of the present application are directed to methods of inhibiting binding of a target protein (T) to a binding protein (P), where a feature of the claimed methods is that this goal is accomplished by having the bifunctional molecule bind direcly to the target protein T. As clearly claimed and explained above, binding of the binding protein (P) to the target protein T to form TP is prevented by producing a tripartite complex T--I--B.

In contrast to the claimed method, in Figure 1 of Varshavsky (which figure is relied upon by the Examiner in maintaining the rejection), the target protein T of the scenario discussed in Figure 1 must, if anything, be I, because I is the protein (enzyme) described in the figure whose activity is to be modulated. Furthermore, the binding protein P (whose binding to I is desired to be selectively inhibited) if anything is i, since it is binding of this moiety to I that one Varshavsky wishes to modulate, as depicted and described in relation to Figure 1.

Varshavsky prevents i from binding to I to form a complex "il" (in the nomenclature of this invention, TP) by covalently bonding i to both "a" and "b", to make his trifunctional molecule. The resulting trifunctional molecule binds to A and/or B (where A and B are both analogous to blocking protein B of the presently claimed methods), i (and the entire trifunctional molecule of which it is a part) is prevented from binding to I. In Varshavsky's method, when the target protein I is prevented from binding to the second protein i, **the trifunctional molecule does not bind to the target protein (T).**

As such, if a tripartite complex is produced in Varshavsky as claimed by the Examiner, this complex is:

A--a-bi--B

I cannot bind to i, because I has been bound to this tripartite complex.

No enzyme I (or target protein T here) is part of the resulting tripartite complex. In contrast, the claimed methods of the present application provide a tripartite complex that includes T.

The claimed invention prevents binding of the target protein T to the binding protein P in a different way: by binding to target protein to the complex and so blocking access to the of the binding protein to the target protein. **In the claimed invention, the bifunctional molecule binds to the target protein and the binding protein P is prevented from binding to the target. As such, the tripartite complex produced by the claimed methods is T--I--B and includes T, in contrast to the methods and abi structure disclosed by Varshavsky.**

Since Varshavsky only teaches or suggests methods in which a trifunctional (not bifunctional) molecule is employed, and binding of the target by the binding protein is accomplished by a mechanism where the trifunctional molecule does not bind to the target protein, Varshavsky fails to anticipate the claims under 35 U.S.C. §102 (b) and this rejection may be withdrawn.

Finally, Claims 22 and 23 remain rejected under 35 U.S.C. § 103(a) over Varshavsky in view of Pouletty, for the asserted reason that Varshavsky taught all of the elements of the claimed method but for the extracellular production of tripartite complexes, which element is assertedly made up by Pouletty.

However, Varshavsky only teaches or suggests the use of a trifunctional compound, a-b-i, and therefore in no way teaches or suggests the use of a bifunctional compound, as is required by the claimed methods.

As Pouletty was been cited solely for the extracellular production site, the Pouletty teaching is incapable of making up the above fundamental deficiency in Varshavsky.

In sum, because the combined teaching of Varshavsky and Pouletty fails to teach or suggest methods of using bifunctional molecule as claimed in Claims 22 and 23, the rejection of Claims 22 and 23 under 35 U.S.C. § 103(a) over Varshavsky in view of Pouletty may be withdrawn.

CONCLUSION

In view of the above amendments and remarks, this application is considered to be in good and proper form for allowance and the Examiner is respectfully requested to pass this application to issuance.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815.

Respectfully submitted,

Date: April 19, 2004

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